CLAIMS

1. A non-human mutant mammal, deficient in an endogenous Sigma receptor, whose genome contains a mutation comprising a disruption in a gene of an endogenous Sigma receptor, wherein said gene disruption gives rise to a non-human mutant mammal lacking detectable levels of endogenous Sigma receptor.

2. Non-human mutant mammal according to claim 1, wherein said non-human mutant mammal is a heterozygous mutant for said mutation.

3. Non-human mutant mammal according to claim 1, wherein said non-human mutant mammal is a homozygous mutant for said mutation.

4. Non-human mutant mammal according to claim 1, wherein said non-human mammal is a mouse.

5. Non-human mutant mammal according to claim 1, wherein the genome of the non-human mutant mammal comprises a transgene within the mutation introduced in the endogenous Sigma-1 receptor gene that comprises a gene encoding a positive selection marker.

6. Non-human mutant mammal according to claim 5, wherein said transgene comprises the neomycin phototransferase (*neo*) gene.

7. Non-human mutant mammal according to claim 1, wherein said Sigma receptor is selected from among a type 1 Sigma receptor (Sigma-1) and a type 2 Sigma receptor (Sigma-2).

8. Non-human mutant mammal according to claim 1, wherein said non-human mutant mammal is a mutant mouse, deficient in the endogenous Sigma-1 receptor, homozygous for the mouse Sigma-1 receptor gene, fertile, whose genome contains a

disruption in said gene comprising the *neo* gene.

9. A homologous recombination vector with positive-negative selection, comprising:

a) A first homology region positioned at the 5' end of a nucleotide sequence encoding a positive selection marker, wherein said first homology region has a nucleotide sequence that is substantially identical to a first sequence of a Sigma receptor gene;

b) A nucleotide sequence encoding a positive selection marker;

c) A second homology region positioned at the 3' end of said nucleotide sequence encoding a positive selection marker, wherein said second homology region has a nucleotide sequence that is substantially identical to a second nucleotide sequence of said Sigma receptor gene, this second sequence of the Sigma receptor gene being positioned at 3' to the first sequence of the Sigma receptor gene in a wild type endogenous Sigma gene; and

d) A nucleotide sequence encoding a negative selection marker.

10. A vector according to claim 9, wherein said Sigma receptor gene is selected from among the type 1 Sigma receptor gene (Sigma-1) and the type 2 Sigma receptor gene (Sigma-2).

11. A vector according to claim 9, wherein said second nucleotide sequence encoding a positive selection marker comprises the neomycin phototransferase (*neo*) gene.

12. A vector according to claim 9, wherein said nucleotide sequence encoding a positive selection marker comprises the thymidin kinase (*tk*) gene of the herpes simplex virus (HSV).

13. A vector according to claim 9, identified as pHR53TK, deposited in CECT with

access number CECT 5737.

14. A host cell whose genome contains an endogenous Sigma receptor gene transfected with a homologous recombination vector with positive-negative selection according to any of claims 9 to 13, deficient in an endogenous Sigma receptor.

15. A cell according to claim 14, wherein said host cell whose genome contains an endogenous Sigma receptor gene is selected from among a differentiated cell that normally expresses the product of the Sigma receptor gene and a pluripotent embryonic cell.

16. A cell according to claim 14, comprising an allele of the mutated Sigma-1 receptor gene.

17. An isolated cell from a non-human mutant mammal, deficient in an endogenous Sigma receptor, according to any of claims 1 to 8, or its offspring.

18. A cell according to claim 17, comprising one or both mutated alleles of the Sigma receptor gene.

19. A cell according to any of claims 17 or 18, propagated and optionally immortalised.

20. The offspring of a non-human mutant mammal deficient in an endogenous Sigma receptor, according to any of claims 1 to 8.

21. A process for making a non-human mutant mammal according to any of claims 1 to 8, comprising the introduction of a functional disruption in an endogenous Sigma receptor gene present in a cell genome by homologous recombination in said cell between an allele of an endogenous Sigma receptor gene and a homologous recombination vector with positive-negative selection according to any of claims 9 to 13, the selection of the recombinant homologues by the positive-negative selection technique, the introduction of said recombinant homologues in embryos, their implantation in receptor pseudogestating

female mammals and their carriage to term, selection of the chimeras able to efficiently transmit the genotype of the recombinant homologues to their offspring by the germ line, crossing said chimeras with non-human wild-type mammals to obtain heterozygous mutants to disrupt the endogenous Sigma receptor and, if desired, crossing of said heterozygous mutants with each other to obtain homozygous mutants.

22. Use of a non-human mutant mammal according to any of claims 1 to 8 as control animals to conduct *in vivo* tests.

23. Use of a non-human mutant mammal deficient in the Sigma-1 receptor, or of a cell line deficient in the Sigma-1 receptor, to evaluate potentially useful compounds meant to

prevent and/or treat disorders of the central nervous system;
prevent and/or treat memory alterations;
prevent and/or treat stress conditions;
prevent and/or treat drug addiction conditions;
produce analgesia; or
produce neuroprotection.

24. Use of a non-human mammal deficient in the Sigma-2 receptor, or of a cell line deficient in the Sigma-2 receptor, for validation and/or development of drugs designed for diagnosis or treatment of cancer, prevention and/or treatment of degenerative processes, or to prevent, reduce or alleviate the side effects associated with the administration of neuroleptic agents.

25. A method for determining the effect of a compound to be tested on a non-human mammal deficient in an endogenous Sigma receptor, which comprises placing in contact a non-human mutant mammal according to any of claims 1 to 8 with said compound and detecting the presence or absence of a physiological change in said non-human mutant mammal in response to the contact with said compound.

26. A method for determining the effect of a compound to be tested on a non-human

mammal deficient in an endogenous Sigma receptor, which comprises administering said compound to be tested to a non-human mutant mammal according to any of claims 1 to 8; administering said compound to be tested to a control non-human mammal expressing a functional endogenous Sigma receptor; and observing if said compound has an effect on the phenotype of said non-human mutant mammal when compared to the control non-human mammal.

27. A method for determining the effect of a compound on cells expressing a Sigma receptor and on cells not expressing said Sigma receptor, which comprises introducing a compound to be tested in a cell population or in a homogenisation thereof, wherein said cells are isolated established cells from a non-human mutant mammal according to any of claims 1 to 8, administering said compound to be tested to a population of the control non-human mammal cells or to a homogenisation thereof, which expresses a functional Sigma receptor, and observing or analysing whether said compound to be tested has an effect on the expression of said Sigma receptor in the cells of said non-human mutant mammal when compared to the cells of a control non-human mammal.